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ELI LILLY AND COMPANY

By D. Leah R. Sanders Date 9/27/2010

PATENT APPLICATION
IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

Appellants	:	Dally, et al.,	Group Art Unit: 1624
Serial No.	:	10/597,241	
International Filing Date	:	January 18, 2005	Examiner: Coleman, B.L.
US National Entry:		July 18, 2006	
Docket No.	:	X-16604M	
For	:	SELECTIVE ESTROGEN RECEPTOR MODULATORS FOR THE TREATMENT OF VASOMOTOR SYMPTOMS	

APPEAL BRIEF (37 C.F.R. § 41.37) FOR DALLY, et al.

Commissioner for Patents
P.O. Box 1450
Alexandria, VA, 22313-1450

Sir:

This brief is in furtherance of the Notice of Appeal, filed in this case on June 25, 2010. Attached hereto is a petition for a one-month extension of time under 37 C.F.R. §1.136. The petition authorizes the Patent Office to charge deposit account No. 05-0840, in the name of Eli Lilly and Company, the necessary fee under 37 C.F.R. §1.17(a)(1) for said one-month extension.

Appellants appeal from the Final Rejection of Claim 1 and its dependent claims 2-13 as well as from the Final Rejection of Claim 18 and its dependent claims 19-28 in the present application under 35 U.S.C. §103(a) and under the judicially created doctrine of Obviousness Type Double Patenting (OTDP), dated March 26, 2010.

The fees required under §41.20 are dealt with in the accompanying FEE TRANSMITTAL sheet.

REAL PARTY IN INTEREST

The Real Party in Interest of the present case is Eli Lilly and Company, Lilly Corporate Center, Indianapolis, Indiana, 46285, as the inventors of the subject matter in the above-referenced application assigned in February 2005 all inventions disclosed in the above referenced application to Eli Lilly and Company.

RELATED APPEALS AND INTERFERENCES

Appellants are aware of no other appeals or interferences which will directly affect, be directly affected by, or have a bearing on the Board's decision in the pending appeal.

STATUS OF CLAIMS

Claim 1 and its dependent claims 2-13 and Claim 18 and its dependent claims 19-28 are currently pending. Claims 14-17 and 29-36 were previously cancelled. In the Office Action dated March 26, 2010, all the pending claims were finally rejected under 35 U.S.C. §35 U.S.C. §103(a) and that final rejection is being appealed. In addition, Claims 1-11, 13, 18-26 and 28 were also finally rejected for OTDP and that final rejection is also being appealed.

STATUS OF AMENDMENTS

No amendments have been submitted subsequent to Final Rejection in the present case.

SUMMARY OF CLAIMED SUBJECT MATTER

Appellants' invention, as embodied in pending claim 1, relates to fluoro-substituted tetracyclic estrogen receptor modulator compounds. See original claims 1-13 on page 125-127 of the specification, original claims 18-28 on pages 127-129, and also the disclosures at page 7, lines 15-22 and page 8, line 15.

GROUNDS OF REJECTION TO BE REVIEWED ON APPEAL

1. Whether claim 1 and its dependent claims 2-13 and Claim 18 and its dependent claims 19-28 were properly rejected under 35 U.S.C. §103(a) in view of

U.S. Patent No.'s 6,133,288 (Grese I); 6,004,971 (Grese II); or 5,726,186 (Grese III) – referred collectively herein as "Grese".

2. Whether claim 1 and its dependent claims 2-5 and claim 18 and its dependent claims 19 and 20 were properly rejected for OTDP over claims 1-3 of Grese II.

3. Whether claim 1 and its dependent claims 2-11, 13 and claim 18 and its dependent claims 19-26 and 28 were properly rejected for OTDP over claims 1-3 of Grese III.

ARGUMENT REGARDING OBVIOUSNESS UNDER 103

In the Office Action of August 24, 2009, the Examiner rejected all of Appellants' pending claims under 35 USC §103(a) over Grese because:

> The generic structure of Grese encompasses the instantly claimed compounds. ... Thus, one of ordinary skill in the art at the time the invention was made would have been motivated to select for example fluoro for the variable R1.

In their reply of December 22, 2009, Appellants traversed the Examiner's rejection:

> The compounds of the present invention as presently (and originally) claimed are directed to fluoro-substituted compounds ... [W]hen one reads beyond the broadest disclosure, Grese teaches a preference for hydroxy or derivatized hydroxy substituted compounds.

Appellants then cited at least ten passages within Grese wherein statements of preference direct the skilled artisan to hydroxy or derivatized hydroxyl compounds. After further pointing out that nearly all of the exemplified compounds within Grese contain hydroxy or derivatized hydroxyl groups and further that Grese did not exemplify any halo compounds, Appellants asserted that "in view of Grese's teachings as a whole, motivation to select fluoro substituted compounds is absent."

In the Final Rejection of March 26, 2010, the Examiner downplayed Appellants' assertions regarding Grese's statements of preference stating that some of those

statements of preference related to chemical intermediates not pertinent to Appellants' claims:

> In the preferred embodiments pointed out by the applicant the protected hydroxys are necessary to prevent reaction at those sites. ... Compounds of the instant invention are within the scope of Grese's formulae I, Ia and Ib and therefore any preferred embodiments with respect to any other formula is not on point. The applicants' attention is drawn to a few other **preferred embodiments** ....

Emphasis added.

First, Appellants respectfully assert that the Examiner has misinterpreted the import of Grese's statements of preference with respect to chemical intermediates not embraced by Appellants' claims. Appellants' overall point with respect to the teaching of Grese is that, although its very broadest disclosure (Grese's compounds of formula I) does relate to halo-substituted compounds, its teachings clearly direct the skilled artisan to hydroxyl or derivatized hydroxy substituted compounds. This point was further evidenced by the fact, as the Examiner acknowledges, that if hydroxy final products are desired, then suitably protected hydroxy chemical intermediates are necessary and by extension (as explicitly stated by Grese) are preferred.

Second, Appellants also respectfully assert that the Examiner's characterization of "a few other preferred embodiments" from Grese is factually inaccurate. The passages cited by the Examiner where fluoro is mentioned among a list of other substituents at R1 does not in fact represent a selection of R1 substituents that includes fluoro but instead is merely reflective of the chronological/logical ordering of the synthetic methodology presented within Grese for the full breadth of what it purports to claim. Beginning from Column 8, line 45, Grese I describes how compounds where R1 is hydrogen, alkoxy, fluoro, chloro, or **protected hydroxyl** are made. That description does not include compounds where R1 is hydroxyl, which Grese later describes as being made from "protected" hydroxyl intermediates at Column 16, line 14. Thus, Grese I's statement at column 16, lines 24-25, relied upon by the Examiner that,

> The above procedures provide, novel, pharmaceutically active compounds of formula I in which R1 [is] hydrogen, hydroxyl, C1-C4 alkoxy, chloro or fluoro.

is not in fact a statement of preference for R1 subsituents but instead merely accurately summarizes the synthetic methodology discussed at that point in Grese I. The remaining R1 compounds from Grese are discussed immediately below the above cited passage:

> Preferred formula la compounds are those in which R1 and R2 each are methoxy, or R1 and R2 each are hydroxyl .... These preferred compounds, as well as other formula Ia compounds, can be used as pharmaceutical agents **or can be further derivitized** to provide other formula I compounds which also are useful for practicing the methods of the present invention.

Emphasis added.

The remaining formula I compounds where synthetic methodology was not specifically addressed at this point in Grese are those where the R1 hydroxy group is derivatized (See Grese Abstract: R1 is OCOC6H5, OCO(C1-C6 alkyl), OSO2(C4-C6 alkyl) and OSO2CF3).

Thus, the Examiner's statement near the end of the final rejection based on obviousness,

> **In view of the preferred embodiment** of formula I where R1 is only ten possible moieties and thus one of ordinary skill in the art would be motivated to select a fluoro moiety for the variable R1 as well as other possiblities from the generically disclosed alternatives of the reference and in so doing obtain the instant compounds **in view of the preferred embodiments outlined above.** Emphasis added

lacks factual foundation and, therefore, Appellants respectfully assert this final rejection based on obviousness is improper.

ARGUMENT REGARDING OTDP

In the Final Rejection of March 26, 2010, the Examiner asserted that Appellants' "compounds are prima facie obvious over [Grese II] and thus the rejection of claims 1-5 and 18-20 are herein maintained" and further that Appellants' "compounds are prima facie obvious over [Grese III] and thus the rejection of claims 1-11, 13,18-26 and 28 are herein maintained.

As laid out fully above, Appellants' respectfully assert that the Examiner prima facie case for obviousness lacks a proper factual foundation and, therefore, this OTDP

rejection is similarly improper. Appellants' respectfully assert that when Grese's overall teachings are considered, (the more than ten statements of preference directing the artisan toward hydroxy or hydroxyl substituted compounds, the lack of exemplification of halo compounds, etc.), a conclusion that the present claims suffer from an OTDP problem in view of Grese II or III is improper.

SUMMARY

For all of the foregoing reasons, Appellants submit that Examiner's rejection of Claims 1-13 and 18-28 under 35 U.S.C. §103(a) was in error and should be reversed. Similarly, Appellants submit that the Examiner's rejections of Claims 1-11, 13, 18-26 and 28 under the judicially created doctrine of OTDP was in error and should be reversed. Appellants respectfully request reversal of the present rejections and passage of the present case to issuance.

Respectfully submitted,

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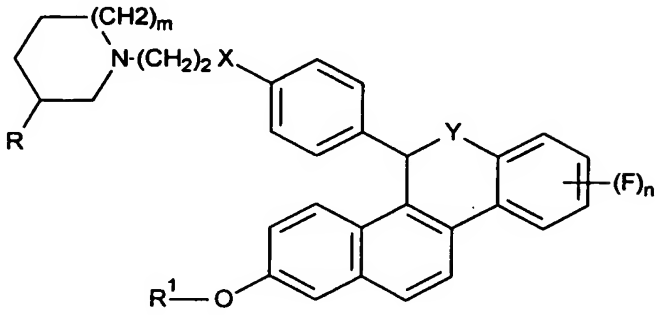
Eli Lilly and Company
Patent Division/GTV
Lilly Corporate Center
Indianapolis, Indiana 46285
September 27, 2010

CLAIMS APPENDIX

1. (Previously presented) A compound of formula I:



(I);

wherein:

m is 0, 1 or 2;

n is 1,2,3or4;

R is H or methyl provided that if m is 1 or 2, then R must be H and that if m is 0, then R must be methyl;

R^1 is H, SO_2 (n-C_4-C_6 alkyl) or COR^2;

X is O or NR^3;

Y is O, S, SO or NR^4;

R^2 is C_1-C_6 alkyl; C_1-C_6 alkoxy; NR^5R^{5a}; phenoxy; or phenyl optionally substituted with halo;

R^3 and R^4 are independently H or C1-C_6 alkyl; and

R^5 and R^{5a} are independently H, C1-C_6 alkyl or phenyl; or a pharmaceutical acid addition salt thereof.

2. (Original) The compound of claim 1 wherein m is 1 or 2.

3. (Previously presented) The compound of claim 2 wherein R1 is H or COR2 and R2 is C1 -C4 alkyl, NHCH3 or phenyl.

4. (Previously presented) The compound of claim 3 wherein R1 is H.

5. (Previously presented) The compound of claim 4 wherein X is O.

6. (Previously presented) The compound of claim 5 wherein Y is 0 or S.

7. (Previously presented) The compound of claim 6 wherein m is 1.

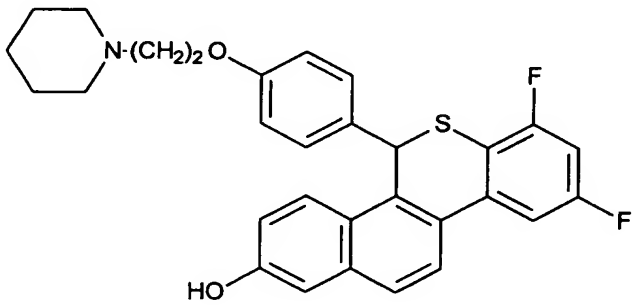
8. (Previously presented) The compound of claim 6 wherein m is 1 and Y is 0.

9. (Previously presented) The compound of claim 6 wherein m is 1 and Y is S.

10. (Previously presented) The compound of claim 9 wherein n is 1, 2 or 3.

11. (Previously presented) The compound of claim 10 wherein n is 1 or 2.

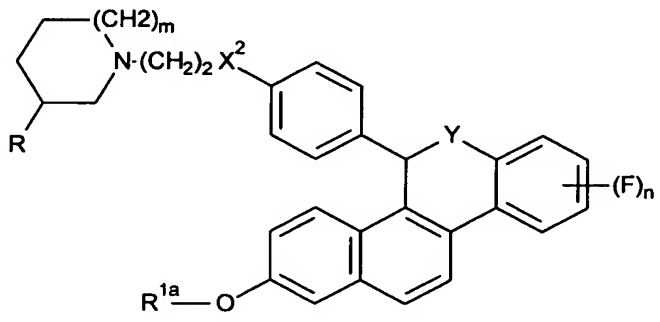
12. (Previously presented) The compound of claim 11 of the formula:



13. (Previously presented) The compound of claim 11 wherein n is 1 and the corresponding fluoro moiety is at the 4-position.

14-17. Cancelled

18. (Previously presented) A compound of formula II



II;

wherein:

m is 0, 1 or 2;

n is 1, 2, 3 or 4;

R is H or methyl provided that if m is 1 or 2, then R must be H and that if m is 0, then R must be methyl;

R^{1a} is H, SO_2CH_3 , SO_2(n-C_4-C_6 alkyl), COR^2, C_1-C_6 alkyl or benzyl;

X^2 is O or NR^7;

Y is O, S, SO or NR^4 ;

R^2 is C_1-C_6 alkyl; C_1-C_6 alkoxy; NR^5R^{5a}; phenoxy; or phenyl optionally substituted with halo;

R^4 is H or C_1-C_6 alkyl;

R^5 and R^{5a} are independently H, C_1-C_6 alkyl or phenyl;

R7 is H, C_1-C_6 alkyl or CO_2(C_1-C_6 alkyl); provided that if R^{1a} is H, SO_2(n-C_4-C_6 alkyl) or COR^2 , then X^2 is NR^7 and R^7 is CO_2 (C_1-C_6 alkyl); or an acid addition salt thereof.

19. (Original) The compound of claim 18 wherein m is 1 or 2 and Rla is SO2CH3, benzyl or methyl.

20. (Previously presented) The compound of claim 19 wherein X2 is O.

21. (Previously presented) The compound of claim 20 wherein Y is O or S.

22. (Previously presented) The compound of claim 21 wherein m is 1.

23. (Previously presented) The compound of claim 21 wherein m is 1 and Y is O.

24. (Previously presented) The compound of claim 21 wherein m is 1 and Y is S.

25. (Previously presented) The compound of claim 24 wherein n is 1, 2 or 3.

26. (Previously presented) The compound of claim 25 wherein n is 1 or 2.

27. (Previously presented) The compound of claim 26 wherein n is 2 and the corresponding fluoro moieties are at the 3- and 5-positions.

28. (Previously presented) The compound of claim 26 n is 1 and the corresponding fluoro moiety is at the 4-position.

29-36. Cancelled

EVIDENCE APPENDIX

None

RELATED PROCEEDINGS APPENDIX

None